Remarks

In response to the Office Action, the applicant hereby makes the following response. The application was filed on 24 Nov. 1998 and included claims 1-50, of which claims 1,8,15,20,25,30,37, and 44 are independent. Claims 15-29 were divided out without prejudice on 26 June 2000, for a later divisional application, if necessary. Accordingly, claims 1-14 and claims 30-50 remain pending for prosecution.

1. Rejection of claims 1-6, 8-13, 30-35, 34-42, 44, 46-50 under 112(1).

With respect to Office Action items #3 and #4, the applicant respectfully disagrees with the Examiner. Concerning analogs or derivatives, a person of ordinary skill in the art would understand what are the analogs or derivatives to testosterone without undue experimentation. The test for enablement is whether "the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." Enzo Biochem v. Calgene, 52 USPQ2d 1129, 1135 (Fed. Cir. 1999); See also, MPEP 2164.01. It is insufficient to allege that all analogs of testosterone are undeterminable without undue experimentation. The burden is on the Examiner to show why reference to "analogs" or "derivatives" of testosterone would require undue experimentation to determine what these are, and must particularly examine the In Re Wands factors, which include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. In Re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In the present case, many working examples of testosterone are given. The nature of the invention is not complex since testosterone and its analogs have been well studied. The specification sets forth in great detail the modalities of action, the combinations, and the modalities of delivery. There is nothing to indicate that the "art is unpredictable" or the like. Furthermore, the amount of experimentation, which applicant contends it not even an issue, is minimal. Basic biochemistry textbooks, that undergraduates use in primary biochemistry classes, outline testosterone, other androgens, other glucocorticoids, other estrogens, etc. Study of these hormones is part of the basic cholesterol utilization and steroid synthesis chapters. Attached are the following: (a) Pg. 656-657 of Biochemistry, by Voet & Voet (1990); and (b) pg. 494-495, of Biochemistry by Stryer (1975) for support for the proposition that cholesterol and testosterone analogs are well known in the art and almost no experimentation would be necessary to determine the analogs. See also, MPEP 2164.02 (sufficiency of examples); 2164.04 (Burden on Examiner to describe the explicit rationale of a lack of enablement). Finally, the applicant notes that at least 10+ testosterone derivatives are stated on pg. 15. Thus, the applicant respectfully requests withdrawal of the enablement rejections.

To the extent that the enablement rejections include "prodrugs" the applicant submits that the prodrugs are adequately described in the specification. Recalling that the enablement is not on whether any experimentation is needed; rather whether the level of experimentation if needed is undue. Thus, the specification teaches on pg. 23 that prodrugs are taught and are further explicated by an expressed reference to the Higuchi and Roche references, the disclosures of which are expressly incorporated to the extent permissible under law. See, pg. 48 of the specification. Hence, the ordinary artisan would have no trouble determining what the prodrugs are because an explicit reference, complete with its citation, is mentioned in the specification. The applicant respectfully requests that the enablement rejections be withdrawn.

2. Rejections of claims 1-14, and 30-50 under 112(1)

With respect to Office Action item #5, the applicant respectfully requests withdrawal of the rejections. The Examiner contends that the claim calls for a method of treating [any level of] serum glucose levels in a patient. The Examiner contends that the specification only teaches a method of treating high levels of serum glucose in a patient. Thus, by inference, the Examiner contends that the claim calls for treatment of any level of serum glucose versus only the "high levels" as taught in the specification.

First, since the claims are claims as originally filed, they are part of the specification and provide for their own enablement. See, 35 USC 112(2). Accordingly, there is a teaching for "any level" of serum glucose because it is taught in the claims themselves.

Second, the specification teaches "any level" of serum glucose. The title of the invention is not restricted to a treatment of high-level serum glucose. The title reflects that the invention is used for the treatment of impaired glucose tolerance and insulin resistance. Similarly, the "Field of the Invention" also does not restrict to high levels. Nothing in the specification teaches or restricts the claimed invention to only hyperglycemia (hyperglycemia being the condition of high glucose in the blood serum). Rather the specification teaches that the invention may be used for hyperglycemia, insulin resistance, and hyperinsulinemia. See, pgs. 15, 18, the Examples (pg. 25-44), etc. Finally, the applicant notes that the disputable language is in the preamble of the claim and that the Examiner has not set forth that the preamble is necessary to breathe life into the claim. While the preamble is not normally considered part of the claim, it is deemed part of the claims where necessary to breathe "life and meaning" into the claims. Corning Glass Works v. Sumitomo Electric U.S.A., 868 F.2d 1251, 9 USPQ2d 1962 (Fed. Cir. 1989). The applicant contends that the "high level" serum glucose is not necessarily nor critical.

3. Rejections of claim 1-14, and 33-50 for indefiniteness.

With respect to Office Action item #6, #7, based on the above arguments, the applicant requests withdrawal of the rejections. As shown above, the term prodrug is used in its ordinary meaning. Accordingly, since the prodrug is in reference to testosterone, it is clear and definite that the term prodrug refers to prodrugs of testosterone. Since the structure of testosterone is clear as understood in the art and as shown on the attached sheets, the applicant contends that "formulae" is understood to mean testosterone and its analogs and/or derivatives.

The applicant notes that claim 7, 14, 36, 43, and 45 are sufficiently definite since the claim calls for the testosterone derivative to comprise dihydrotestosterone. The word "comprises" indicates open endedness. Stiftung v. Renishaw PLC, 945 F.2d 1173, 1178, 20 USPQ2d 1094 (Fed. Cir. 1991). As such, the claim should be read as being that the testosterone of claim 1 includes, among other things, dihydrotestosterone. This reading does not limit the "other things" that may be present. All that is required in the claim is that at least, that the testosterone of claim 1 is the dihydro form. The Examiner's queries are unduly restrictive and do not reflect the claim scope.

With respect to claims 44-50, claim 44 has been amended to delete the identification portion.

With respect of Office Action item #8, the applicant has amended the claims, where appropriate to add the proper antecedent basis.

With respect to Office Action item #9, the applicant notes that the term "including" and "includes" is an open-ended term; akin to "comprising". Thus, a claim such as a "widget including A" means that the widget has A plus other things. Burke v. Everest Jennings, 29 USPQ2d 1393, 1397 (Fed. Cir. 1993)(unpublished) ("As a general rule, "comprising" and

"including" are open-ended terms which cover the structural elements recited plus additional elements. See 2 D. Chisum, Patents, Section 8.06 [1] (1992)."). The applicant queries why the claims are indefinite for using time-accepted claim language.

With respect to other amendments, other claims were amended to merely delete the word "thereof" which was repeated twice, such as in "... thereof thereof...".

4. Rejection of Claims Under Sect. 102.

The independent claims were amended, if appropriate, to include the limitation that an additional step of identifying a human subject exhibiting abnormal insulin resistance is claimed. Coleman discusses the use of DHEA in mice. Nothing suggests or teaches that his disclosure may be applicable to humans. In fact, the only suggestion or teaching of future uses of the Coleman disclosure is that Coleman suggests more experimentation on aging non-obese mice. Since Coleman specifically fails to include the limitation of identifying insulin resistance in humans, it cannot, as a matter of law, anticipate the claimed invention.

Mauriello does not anticipate nor does it render the claimed invention obvious. First, nothing in Mauriello teaches selecting the patients based on a predetermined testosterone ratio. On this basis alone, the invention distinguishes over Mauriello. Second, the reference is oriented to a different problem and proposes different solutions. Third, nothing in the reference suggests that it can be combined with other references to obtain the claimed invention. Coleman deals with using DHEA (not even testosterone) in mice. Moller involves the treatment of cardiovascular disease and not insulin resistance. Accordingly, since the problems identified are different from the problem solved by the claimed invention, the claimed invention is not obvious. See In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999)(Evidence of a suggestion, teaching, or motivation to combine prior art references may flow, inter alia, from the

references themselves, the knowledge of one of ordinary skill in the art, or from the nature of the problem to be solved.).

Similarly, Moller for the above reasons fails to invalidate the claims. Moller's entire teaching is about cardiovascular disease. In the 82 pages of disclosure, the only one statement mentioned by Examiner concerns application of anabolic steroids to insulin resistant patients. The Moller reference does not teach selecting patients with insulin resistance and selecting them based on testosterone ratios. The Moller reference deals with the treatment of cardiovascular disease and does not even remotely suggest the claimed invention. It too involves completely unrelated problems and solutions.

In addition, one nature of the invention is to determine useful and effective amounts for therapy. While the Examiner asserts that it would have been obvious to tinker with the prior art to determine the effective amount, there is no suggestion in the references to do so. If the Examiner asserts that it is well-known in the Examiner's knowledge to do so, then the applicant respectfully requests the Examiner execute an affidavit that shall be as specific as possible, complete with reference to supporting materials. See, 37 CFR 1.104(d)(2).

Finally, nothing in the cited references discuss identifying hemoglobin A1C and administering testosterone to treat conditions related thereto. The absence of a claimed element is ipso facto not anticipated or obvious because of the missing element. Accordingly, while various references may discuss testosterone, diabetes, this alone does not mean that hemoglobin A1C is even implicated. Again, if the Examiner has particular knowledge thereto, the affidavit requested must also address this. Along the same lines, the references do not suggest or disclose sex hormone binding globulins, measurements thereof, assaying thereof. Along the same lines, the references fail to discuss or disclose Syndrome X in the same manner as the claimed invention.

Thus, the amendments sufficiently distinguish over the art, where applicable. None of the art anticipates nor renders the claimed invention obvious. Re-examination is therefore respectfully requested.

Conclusion

The applicant respectfully requests withdrawal of the rejections and believes that the claims as presented represent allowable subject matter. However, if the Examiner desires, the applicant is ready for a telephone interview to expedite prosecution. As always, the Examiner is free to call the undersigned at 312-876-2622. The Examiner's attention is also drawn to the new correspondence address.

Respectfully submitted,

By its attorney,

Shashank Upadhye

Shashank Upadhye
(Certificate of recognition attached)

Date: Dec. 15, 2000

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To:

Our parents, who encouraged us,
Our teachers, who enabled us, and
Our children, who put up with us.

Cover Art: One of a series of color studies of horse heart cytochrome *c* designed to show the influence of amino acid side chains on the protein's three-dimensional folding pattern. We have selected this study to symbolize the discipline of biochemistry: Both are beautiful but still in process and hence have numerous "rough edges." Drawing by Irving Geis in collaboration with Richard E. Dickerson.

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high cholesterol diet. FH is a dominant genetic defect that results in a deficiency of functional LDL receptors (Section 11-4C). Homozygotes for this disorder lack functional LDL receptors so that their cells can absorb neither IDL nor LDL by receptor–mediated endocytosis. The increased concentration of IDL in the bloodstream leads to a corresponding increase in LDL which is, of course, underutilized since it cannot be taken up by the cells (Fig. 23-49*b*). FH homozygotes therefore have plasma LDL–cholesterol levels three to five times higher than average. FH heterozygotes, which are far more common, have about one half of the normal number of functional LDL receptors and plasma LDL–cholesterol levels of about twice the average.

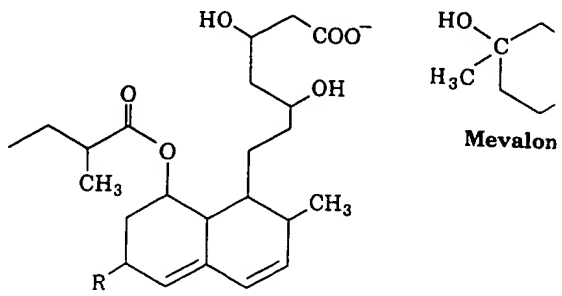
The ingestion of a high cholesterol diet has an effect similar, although not as extreme, as FH (Fig. 23-49c). Excessive dietary cholesterol enters the liver cells in chylomicron remnants and represses the synthesis of LDL–receptor protein. The resulting insufficiency of LDL receptors on the liver cell surface has consequences similar to those of FH.

LDL receptor deficiency, whether of genetic or dietary origin, raises the LDL level by two mechanisms: (1) increased LDL production resulting from decreased IDL uptake; and (2) decreased LDL uptake. Two strategies for reversing these conditions (besides maintaining a low cholesterol diet) have been tested:

1. *Ingestion of resins that bind bile acids thereby preventing their intestinal absorption.* Bile acids are normally efficiently recycled by the liver (Section 23-6C). Elimination of resin-bound cholesterol in the feces forces the liver to convert more cholesterol to bile acids than normal. The consequent decrease in the serum cholesterol concentration induces synthesis of LDL receptors (of course, not in FH homozygotes). Unfortunately, the decreased serum cholesterol level also induces the synthesis of HMG-CoA reductase, which increases the rate of cholesterol biosynthesis. Ingestion of bile acid-binding resins therefore provides only a 15 to 20% drop in serum cholesterol levels.

2. *Treatment with competitive inhibitors of HMG-CoA reductase, notably the fungal products compactin and lovastatin (also called mevinolin; Fig. 23-50), so as to decrease the rate of cholesterol biosynthesis.* Indeed, lovastatin has recently received clinical approval for the treatment of hypercholesterolemia. The resulting decreased cholesterol supply is again met by induction of LDL receptors and HMG-CoA reductase. Lovastatin-treated FH heterozygotes nevertheless routinely show a serum cholesterol decrease of 30%.

The combined use of these agents, moreover, results in a clinically dramatic 50 to 60% decrease in serum cholesterol levels.



Mevalon

R = H Compactin
R = CH_3 Lovastatin

Figure 23-50
Compactin and lovastatin, two potent inhibitors of HMG reductase. The structure of mevalonate is shown for comparison.

C. Cholesterol Utilization

Cholesterol is the precursor of steroid hormones and bile acids. Steroid hormones are grouped into five categories: ***progestins, glucocorticoids, mineralocorticoids, androgens, and estrogens.*** These hormones, described in Section 34-4A, mediate a wide variety of vital physiological functions. All contain the four-ring structure of the sterol nucleus and are remarkably similar in structure, considering the enormous differences in their physiological effects. A simplified biosynthetic scheme (Fig. 23-51) indicates their structural similarities and differences. We shall not discuss the details of these pathways.

The quantitatively most important pathway for the excretion of cholesterol in mammals is the formation of bile acids (also called bile salts). The major bile acids, **cholic acid and chenodeoxycholic acid,** are synthesized in the liver and secreted as glycine or taurine conjugates (Fig. 23-52) into the gallbladder. From there, they are secreted into the small intestine where they act as emulsifying agents in the digestion and absorption of the fat-soluble vitamins (Section 23-1). An efficient recycling system allows the bile acids to reenter the bloodstream and return to the liver for reuse several times each day. The $< 1\ g \cdot day^{-1}$ of bile acids that escape this recycling system are further metabolized by microorganisms in the large intestine and excreted. ***This is the body's only route for cholesterol excretion.***

Comparison of the structures of cholesterol and the bile acids (Figs. 23-34 and 23-52) indicates that the synthesis of bile acids from cholesterol involves (1) reduction of the 5,6-double bond, (2) epimerization of the 3β-OH group, (3) introduction of OH groups at the 7α and 12α positions, (4) oxidation of C(24) to a carboxylate, and (5) conjugation of this side chain with glycine or taurine.

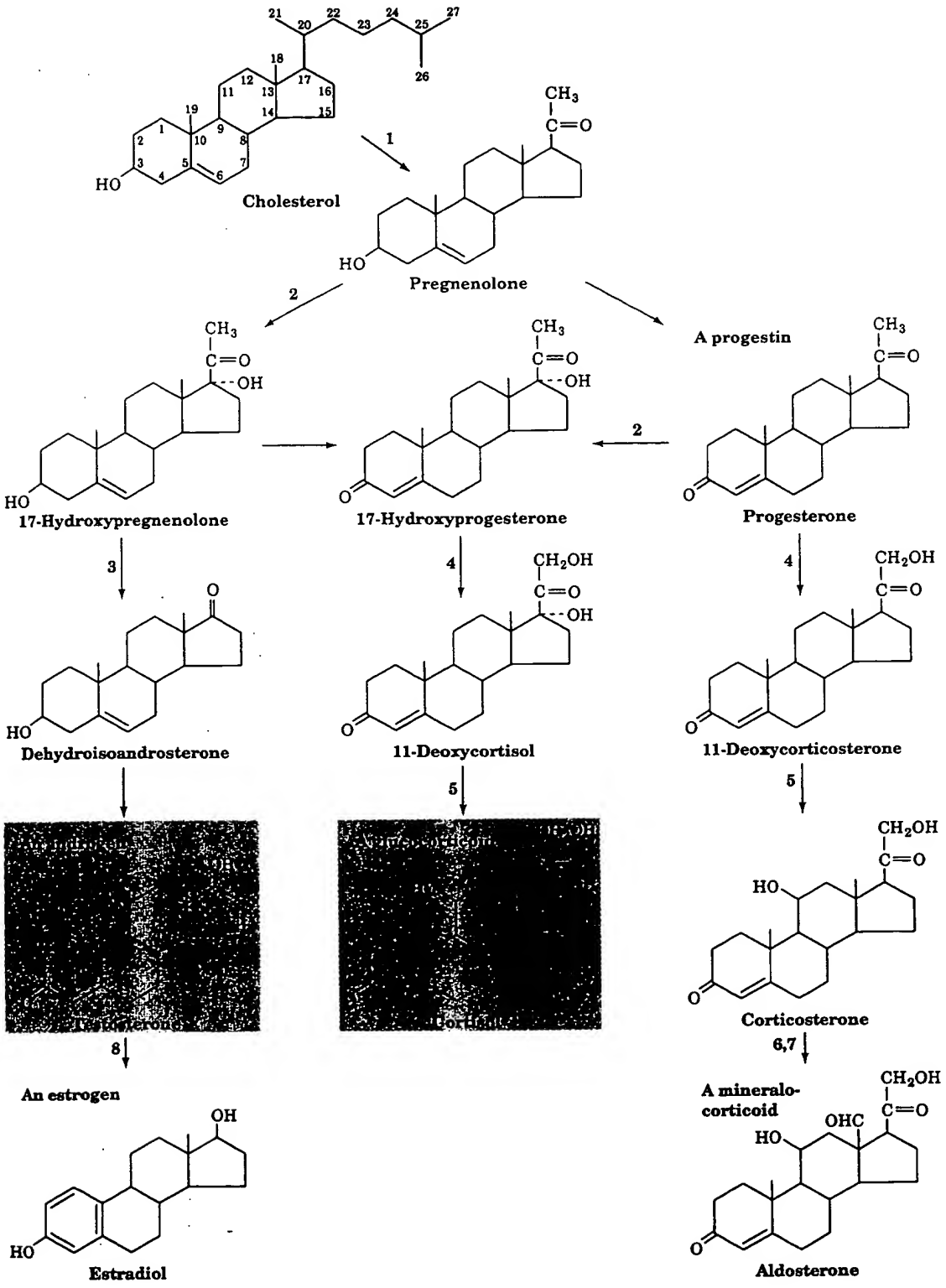


Figure 23-51
A simplified scheme of steroid biosynthesis. The enzymes involved are (1) the cholesterol side chain cleavage enzyme; (2) steriod C(17) hydroxylase; (3) steroid C(17),C(20) lyase; (4) steroid C(21) hydroxylase; (5) steroid 11β-hydroxylase; (6) steroid C(18) hydroxylase; (7) 18-hydroxysteroid oxidase; and (8) aromatase.

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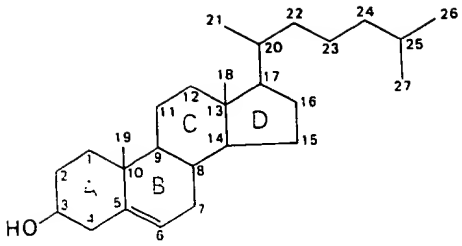
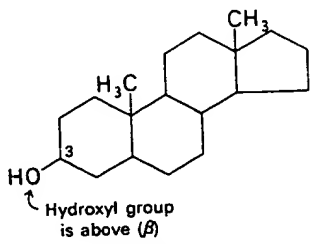


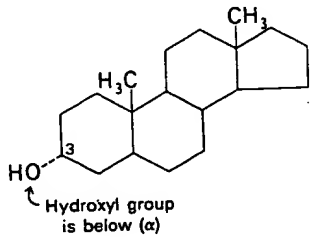
Figure 20-15
Numbering of the carbon atoms of cholesterol.

NOMENCLATURE OF STEROIDS

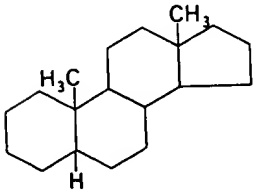
A few comments concerning steroid nomenclature are appropriat before turning to the synthesis of steroid hormones. Carbon aton in steroids are numbered as shown in Figure 20-15 for cholestero The rings in steroids are named A, B, C, and D. Cholesterol con tains two angular methyl groups: the C-19 methyl group is attache to C-10, and the C-18 methyl group is attached to C-13. A lin above C-10 or C-13 denotes a methyl group. By definition, the C-1 and C-19 methyl groups of cholesterol are *above* the plane containin the four rings. A substituent that is above the plane is termed *β-oriented,* and is shown by a *solid* bond. In contrast, a substituen that is below the plane is *α-oriented* and denoted by a *dashed* dotted line.



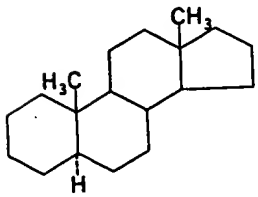
3β-Hydroxy



3α-Hydroxy



5β-Hydrogen
(A *cis* fusion)



5α-Hydrogen
(A *trans* fusion)

A hydrogen atom attached to C-5 can be α- or β-oriented. Wh this hydrogen atom is *α-oriented,* the A and B rings are fused a *trans* conformation, whereas a *β-orientation* yields a *cis* fusion. T absence of a symbol for the C-5 hydrogen atom implies a *tr* fusion. The C-5 hydrogen atom is α-oriented in all steroid hormo that contain a hydrogen atom in that position. In contrast, b salts have a β-oriented hydrogen atom at C-5. Thus, *a* cis *fus is characteristic of the bile salts, whereas a* trans *fusion is characteri of all steroid hormones that possess a hydrogen atom at C-5.* A *trans* fusi yields a nearly planar structure, whereas a *cis* fusion gives a buck structure.

STEROID HORMONES ARE DERIVED FROM CHOLESTEROL

Cholesterol is the precursor of the five major classes of ster hormones: progestagens, glucocorticoids, mineralocorticoids,

rogens, and estrogens (Figure 20-16). *Progesterone,* a *progestagen,* repares the lining of the uterus for implantation of an ovum. rogesterone is also essential for the maintenance of pregnancy. *ndrogens* (such as *testosterone*) are responsible for the development f male secondary sex characteristics, whereas *estrogens* (such as *strone*) are required for the development of female secondary sex haracteristics. Estrogens also participate in the ovarian cycle. *lucocorticoids* (such as *cortisol*) promote gluconeogenesis and the ormation of glycogen, and also enhance the degradation of fat and rotein. *Mineralocorticoids* (such as *aldosterone*) cause increased re-bsorption of Na^+, Cl^-, and HCO_3^- by the kidney, which leads o an increase in blood volume and blood pressure. The major ites of synthesis of these classes of hormones are: progestagens, orpus luteum; estrogens, ovary; androgens, testis; glucocorticoids nd mineralocorticoids, adrenal cortex.

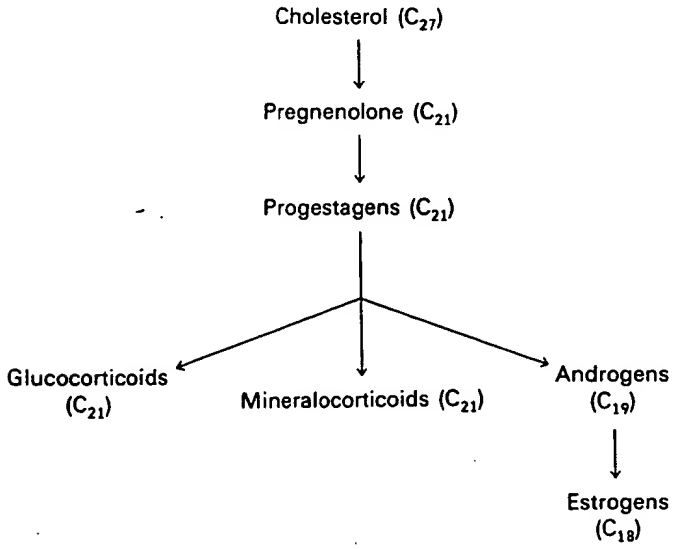


Figure 20-16
Biosynthetic relationships of steroid hormones.

STEROIDS ARE HYDROXYLATED BY MIXED-FUNCTION OXIDASES THAT UTILIZE NADPH AND O_2

Hydroxylation reactions play a very important role in the conversion of cholesterol to steroid hormones and bile salts. All of these hydroxylations require *NADPH and* O_2. The oxygen atom of the